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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

The applicant has submitted this efficacy supplement along with a request for pediatric exclusivity determination. FDA issued a Written Request for pediatric studies for temsirolimus on January 12, 2001 and subsequently reissued and amended it. The applicant submitted the results from a Phase I/II study in pediatric patients with relapsed/refractory solid tumors. The study did not show efficacy of temsirolimus in pediatric patients with neuroblastoma, rhabdomyosarcoma and high-grade gliomas with respect to objective response rate. However, the applicant fulfilled the requirements of the Written Request.

This application is based on a single Phase I/II, open-label, 2-part study of temsirolimus given as a 60-minute IV infusion once weekly in 3-week cycles to pediatric subjects with advanced solid tumors (protocol 3066K1-139-US, CSR-76631). The study had two parts. Part 1 was an ascending-dose study in subjects aged 1 to 21 years with advanced solid tumors to determine the maximum tolerated dose (MTD) of temsirolimus. Part 2 was aimed at verifying the safety of the dose selected in part 1 and at obtaining preliminary data on antitumor activity of temsirolimus in 3 groups of children with refractory or relapsed pediatric solid tumors: neuroblastoma, rhabdomyosarcoma, and high-grade gliomas. Part 2 of the study used a Simon's 2 stage design for each tumor category. The sample size was based on the response probability of an ineffective drug of 0.08, the response probability of an effective drug of 0.30, probability of accepting an ineffective drug = 0.10, and the probability of rejecting an effective drug = 0.10. For each group, the sample size for the first stage was at least 12 evaluable subjects, and the sample size for the second stage was at least 13 evaluable subjects. For each tumor type, if after the first stage, there were fewer than 2 responses, then temsirolimus was to be considered an ineffective drug for that tumor type and enrollment in the group was to be stopped. Otherwise, the trial was to continue until 25 evaluable subjects were enrolled. Temsirolimus would be considered for further development in phase 2 and 3 trials only if at least 4 evaluable subjects had an objective response within 12 weeks.

Nineteen and 52 patients were enrolled in part 1 and part 2, respectively. In part 2, 19 patients had neuroblastoma, 16 had rhabdomyosarcoma and 17 had high-grade gliomas. Efficacy was not a primary objective in part 1. Objective response rate (ORR) was the primary efficacy endpoint in part 2.

There was only one partial response in the neuroblastoma tumor type in part 2 [ORR = 5.26%, exact 95% CI: (0.13%, 26.03%)]. Other tumor categories in part 2 did not have any responses. The number and percentages of patients for each response category and ORR with 95% exact confidence intervals are presented in Table 2.

2. INTRODUCTION

2.1. Overview

In the United States, approximately 12,400 children and adolescents younger than 20 years of age are diagnosed with some type of cancer each year. Among these, approximately 2300 children and adolescents die of cancer each year, making cancer the most common cause of disease-related mortality for children 1 to 19 years of age. There are 12 major types of childhood cancers, and of these leukemias and brain and other central nervous system (CNS) tumors (ie, gliomas and medulloblastomas) account for over 50% of the new cases. The remainder of new cases includes extracranial tumors, such as neuroblastomas, Wilms tumors, and rhabdomyosarcomas.

2.1.1. Regulatory History

The NDA 22088 for Torise (temsirolimus) injection was submitted on 5 October 2006 and was approved on 30 May 2007 for the treatment of advanced renal cell carcinoma. FDA issued a Written Request for pediatric studies for temsirolimus on January 12, 2001 and reissued it under Best Pharmaceuticals for Children Act on September 30, 2004. FDA subsequently issued amendments to the Written Request dated September 28, 2007, September 29, 2010 and February 25, 2011. All amendments only extended the timeframe for submitting the report of the study.

This application is based on a single Phase I/II study (protocol 3066K1-139-US, CSR-76631). The study was conducted under IND 55,830.

2.1.2. Specific Studies Reviewed

This application is based on a single Phase I/II study (protocol 3066K1-139-US, CSR-76631). The study was a safety and exploratory pharmacodynamic study of intravenous temsirolimus in pediatric subjects with relapsed/refractory solid tumors.

2.2. Data Sources

Data used for this review are from the electronic submission dated December 2, 2011. The path is [\\Cdsesub1\EVSPROD\NDA022088\0083\m5\datasets\study-139-progress-report\listings\](\\Cdsesub1\EVSPROD\NDA022088\0083\m5\datasets\study-139-progress-report\listings).

3. STATISTICAL EVALUATION

3.1. Data and Analysis Quality

Overall the data and analysis quality of the submission was acceptable for the reviewer to be able to perform the statistical review.

3.2. Evaluation of Efficacy

The applicant has submitted efficacy results from one Phase I/II study (protocol 3066K1-139-US, CSR-76631) titled “A Phase 1/2 safety and exploratory pharmacodynamic study of intravenous temsirolimus (CCI-779) in pediatric subjects with relapsed/refractory solid tumors”. This review is primarily based on the Phase II portion of the study.

3.2.1. Study Objectives

3.2.1.1. Primary Objective

Part 1: The primary objective of part 1 of the study was to evaluate the safety of intravenous (IV) temsirolimus given once weekly to children with solid tumors with disease that was recurrent or refractory to standard therapy or for whom standard therapy was not available.

Part 2: The primary objective of part 2 was to obtain preliminary information on the anti-tumor activity (assessed by objective response rate within 12 weeks) of IV temsirolimus in children with relapsed/refractory neuroblastoma, high-grade gliomas, and rhabdomyosarcoma.

3.2.1.2. Secondary Objectives

The secondary objectives for part 1 were to:

- Identify the maximum tolerated dose (MTD) or a biologically effective dose of IV temsirolimus when administered once weekly.
- Obtain preliminary information on the antitumor activity of IV temsirolimus.
- Determine the single- and multiple-dose pharmacokinetics (PK) of temsirolimus in children with once-weekly IV treatment.
- Determine the effects of IV temsirolimus on changes in the mammalian target of rapamycin (mTOR) signaling pathway in the peripheral blood mononuclear cells (PBMCs).

The secondary objectives for part 2 were to:

- Verify the safety of the selected dose.
- Evaluate the percentage of subjects exhibiting freedom from progression (ie, disease stabilization) at 3 months.

- Determine the single and multiple-dose pharmacokinetics of temsirolimus in children with once-weekly IV treatment.
- Determine the effects of IV temsirolimus on changes in the mTOR signaling pathway in the bone marrow.

3.2.2. Study Design

This was an open-label, 2-part study of temsirolimus given as a 60-minute IV infusion once weekly in 3-week cycles to pediatric subjects with advanced solid tumors. Premedication with IV diphenhydramine 1 mg/kg (or comparable antihistamine) was to be given approximately 30 minutes before the start of each temsirolimus infusion. Part 1 was an ascending-dose study in subjects aged 1 to 21 years with advanced solid tumors to determine the maximum tolerated dose (MTD) of temsirolimus. The MTD was defined as the dose level at which ≥ 2 of 3 subjects, or ≥ 2 of 6 subjects if the dose level had been expanded, experience a dose limiting toxicity (DLT) by day 21 after the first dose of temsirolimus.

Part 2 was aimed at verifying the safety of the dose selected in part 1 and at obtaining preliminary data on antitumor activity of temsirolimus in 3 groups of children with refractory or relapsed pediatric solid tumors: neuroblastoma, rhabdomyosarcoma, and high-grade gliomas.

In both parts, subjects were considered to have completed the study if they have received 6 months of temsirolimus. After 6 months of treatment, at the discretion of the principal investigator and sponsor, subjects who had not progressed and who were tolerating treatment could remain on temsirolimus as long as there was continued evidence of clinical benefit.

3.2.3. Efficacy Endpoints

Efficacy was not a primary objective in part 1. The following efficacy endpoints were used in part 2.

Primary endpoint:

- Objective response rate (ORR)

Secondary endpoint:

- Rate of freedom from progression at 3 months

ORR is defined as the proportion of subjects with complete response (CR) or partial response (PR) within 12 weeks of treatment.

Rate of freedom from progression at 3 months was defined as the proportion of subjects having disease stabilization. For subjects with neuroblastoma, disease stabilization included the following tumor responses: CR, very good partial response (VGPR), mixed response (MR), PR, and stable disease (SD). For subjects with gliomas and rhabdomyosarcomas, disease stabilization included CR, PR, and SD.

The measurability of a tumor was defined by the Response Evaluation Criteria In Solid Tumors (RECIST) classification. At study entry, subjects were to have at least one measurable lesion. For rhabdomyosarcoma and glioma, the evaluation of target and non-target lesions was based on RECIST guidelines. Subjects diagnosed with neuroblastoma were to be evaluated with 1) RECIST investigator provided assessments derived from target and non-target responses, + 2) bone marrow results, if available, + 3) Homovanillac acid (HVA) and Vanillymandelic acid (VMA) results if available, + 4) metaiodobenzylguanidine (MIBG) central reader global evaluations. If results 2 and 3 were unavailable, they were assumed to be normal/OK; if either 1 or 4 results were unavailable, the available results were to be used to indicate response. If neither 1 nor 4 results were available then the neuroblastoma subject was non-evaluable for response at that time point. Primary efficacy response for the neuroblastoma cohort was to be achieved programmatically and corroborated with a clinical analysis of response, based on International Neuroblastoma Staging System (INSS) criteria, using available data where appropriate. The evaluation of response by the treating institution using MIBG scan used the International Neuroblastoma Response Criteria (INRC).

Freedom-from-progression at 3 months was the secondary efficacy measure. Subjects who were assessed at SD or better, and who were not evaluated as having PD during the 3 months were considered to be free from progression. Subjects diagnosed with neuroblastoma were assessed as specified above. Subjects with a diagnosis other than neuroblastoma used RECIST investigator-provided responses for secondary efficacy assessment.

3.2.4. Sample Size Considerations

In part 1 of the study, subjects were to be assigned sequentially to 1 of 4 dose groups: 10, 25, 75 or 150 mg/m². At least 3 to 6 subjects were to be enrolled at each dose level. Dose escalation to the next level occurred based on safety evaluation for at least 3 weeks after the first dose of temsirolimus for all subjects at a particular dose level. A minimum of 6 subjects were to be treated with the MTD of temsirolimus.

The study design of part 2 was based on the Simon 2-stage design. The sample size was based on the response probability of an ineffective drug of 0.08, the response probability of an effective drug of 0.30, probability of accepting an ineffective drug = 0.10, and the probability of rejecting an effective drug = 0.10. For each group, the sample size for the first stage was at least 12 evaluable subjects, and the sample size for the second stage was at least 13 evaluable subjects.

For each tumor type, if after the first stage, there were fewer than 2 evaluable subjects with an objective response within 12 weeks, then temsirolimus was to be considered an ineffective drug for that tumor type and enrollment in that group was to be stopped. Otherwise, the trial was to continue until 25 evaluable subjects were enrolled. Temsirolimus would be considered for further development in phase 2 and 3 trials only if at least 4 evaluable subjects had an objective response within 12 weeks.

Reviewer's comment:

None of the tumor types met the criteria to move to the second stage of Simon's two-stage design and the enrollment in each group was stopped after stage 1.

3.2.5. Sponsor's Results and FDA Statistical Reviewer's Findings/Comments

The intent-to-treat (ITT) population included all patients who were enrolled in the study. The efficacy evaluable (EE) population included all patients who received at least 3 doses (i.e., 1 cycle) of temsirolimus.

There were 19 patients in part 1 and 52 patients in the part 2 of the study of which 18 and 42 were efficacy evaluable in part 1 and part 2, respectively. In part 1, 4 subjects received 10 mg/m² dose, 5 subjects received 25 mg/m², 3 subjects received 75 mg/m² and 7 subjects received 150 mg/m². There were 52 evaluable subjects in part 2, including 19 subjects with neuroblastoma, 16 subjects with rhabdomyosarcoma, and 17 subjects with high-grade gliomas, who were treated with 75 mg/m² of temsirolimus IV once weekly.

3.2.5.1. Baseline Characteristics

A summary of demographic characteristics at baseline is presented in Table 1.

Table 1: Demographic Characteristics: Gender, Race, Age at Study Entry and Geographic Region

| | | Part 1 (N=19) | Part 2 (N=52) | All (N=71) |
|------------------------------|----------|--------------------------|--------------------------|-----------------------|
| Gender | Female | 8 (42%) | 17 (33%) | 25 (35%) |
| | Male | 11 (58%) | 35 (67%) | 46 (65%) |
| Race | White | 13 (68%) | 34 (65%) | 47 (66%) |
| | Black | 3 (16%) | 10 (19%) | 13 (18%) |
| | Asian | 0 (0%) | 1 (2%) | 1 (1%) |
| | Hispanic | 2 (11%) | 3 (6%) | 5 (7%) |
| | Other | 1 (5%) | 3 (6%) | 4 (6%) |
| | Unknown | 0 | 1 (2%) | 1 (1%) |
| Age in Years at Entry | Mean | 12.1 | 9.5 | 10.2 |
| | Median | 11 | 8 | 9 |
| | Min, Max | 4, 21 | 1, 21 | 1, 21 |
| Geographic region | US | 19 (100%) | 43 (83%) | 62 (87%) |
| | Non-US | 0 (0%) | 9 (17%) | 9 (13%) |

3.2.5.2. Primary Efficacy Analysis

The primary endpoint for part 2 was ORR. There was only 1 partial response observed in a 4-year old neuroblastoma patient. The ORR in neuroblastoma category was 5.26% with an exact 95% CI: (0.13%, 26.03%). The ORR in the overall ITT population was 1.92% (exact 95% CI: [0.05%, 10.26%]) in part 2. None of the tumor types met the criteria to move to the second stage of Simon's two-stage design and the enrollment in each group was stopped after stage 1. The number and percentage of patients in each response category and ORR with a 95% exact confidence interval for the ITT population are shown in Table 2.

Table 2: Response Categories in Part 2 in the ITT Population

| | Neuroblastoma (N=19) | Rhabdomyo- sarcoma (N=16) | High Grade Gliomas (N=17) | All (N=52) |
|--|--------------------------|---------------------------------|---------------------------------|-------------------------|
| Complete Response | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Partial Response | 1 (5%) | 0 (0%) | 0 (0%) | 1 (2%) |
| Stable Disease | 7 (37%) | 4 (25%) | 7 (41%) | 18 (36%) |
| Progressive Disease | 10 (53%) | 9 (56%) | 6 (35%) | 25 (48%) |
| Unknown | 1 (5%) | 3 (19%) | 4 (24%) | 8 (15%) |
| Objective Response Rate (Exact 95% CI) | 5.26% (0.13%, 26.03%) | 0% (0%, 20.59%) | 0% (0%, 19.51%) | 1.92% (0.05%,10.26%) |

In part 1, one subject had CR, 7 had SD and 8 had PD. For 2 subjects response to treatment was considered unknown because the tumor assessment was performed after less than 37 days of treatment.

Reviewer's Comment:

Temsirolimus administered weekly at the dose of 75 mg/m² was determined to have insufficient efficacy in children with neuroblastoma, rhabdomyosarcoma, and high-grade gliomas.

3.3. Evaluation of Safety

For a detailed safety evaluation, please refer to the clinical review of this application.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

With a small sample size (19 in part 1 and 52 in part 2), findings in subgroups are not meaningful. Therefore, this section is not applicable for this application.

5. SUMMARY AND CONCLUSIONS

This application is based on a single Phase I/II, open-label, 2-part study of temsirolimus given as a 60-minute IV infusion once weekly in 3-week cycles to pediatric subjects with advanced solid tumors (protocol 3066K1-139-US, CSR-76631). The study had two parts. Part 1 was an ascending-dose study in subjects aged 1 to 21 years with advanced solid tumors to determine the maximum tolerated dose (MTD) of temsirolimus. Part 2 was aimed at verifying the safety of the dose selected in part 1 and at obtaining preliminary data on antitumor activity of temsirolimus in 3 groups of children with refractory or relapsed pediatric solid tumors: neuroblastoma, rhabdomyosarcoma, and high-grade gliomas. Part 2 of the study used a Simon's 2 stage design for each tumor category. The sample size was based on the response probability of an ineffective drug of 0.08, the response probability of an effective drug of 0.30, probability of accepting an ineffective drug = 0.10, and the probability of rejecting an effective drug = 0.10. For each group, the sample size for the first stage was at least 12 evaluable subjects, and the sample size for the second stage was at least 13 evaluable subjects. For each tumor type, if after the first stage, there were fewer than 2 responses, then temsirolimus was to be considered an ineffective drug for that tumor type and enrollment in the group was to be stopped. Otherwise, the trial was to continue until 25 evaluable subjects were enrolled. Temsirolimus would be considered for further development in phase 2 and 3 trials only if at least 4 evaluable subjects had an objective response within 12 weeks.

Nineteen and 52 patients were enrolled in part 1 and part 2, respectively. In part 2, 19 patients had neuroblastoma, 16 had rhabdomyosarcoma and 17 had high-grade gliomas. Efficacy was not a primary objective in part 1. Objective response rate (ORR) was the primary efficacy endpoint in part 2.

There was only one partial response in the neuroblastoma tumor type in part 2 [ORR = 5.26%, exact 95% CI: (0.13%, 26.03%)]. Other tumor categories in part 2 did not have any responses.

5.1. Conclusions and Recommendations

The applicant has submitted this efficacy supplement along with a request for pediatric exclusivity determination. FDA issued a Written Request for pediatric studies for temsirolimus on January 12, 2001 and subsequently reissued and amended it. The applicant submitted the results from a Phase I/II study in pediatric patients with relapsed/refractory solid tumors. The study did not show efficacy of temsirolimus in pediatric patients with neuroblastoma, rhabdomyosarcoma and high-grade gliomas with respect to objective response rate. However, the applicant fulfilled the requirements of the Written Request.

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